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Restorbio clutches at straws, and investors say that’s fine

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The win Restorbio is claiming in a mid-stage study is by no means clear-cut.

Perhaps the only way to make sense of Restorbio’s share price surge this morning is to see it in the context of a stock that had already lost 40% of its value since the company floated in January. Little in today’s clinical data release covering the group's lead asset, RTB101, suggests an unequivocal win.

This of course has not stopped Restorbio from trumpeting the phase II result as positive, statistically significant and clinically meaningful. Serious investors will want a better explanation about why only one RTB101 dose showed efficacy, and why neither a high dose nor a combination with a similarly acting drug worked.

Restorbio’s phase II trial aimed to reduce the incidence of respiratory tract infections in elderly patients, 652 of whom had been enrolled into the two-stage study. Effectively, this resulted in four dosing regimens of RTB101 being tested: 5mg once daily, 10mg once daily, 10mg twice daily and 10mg plus Novartis’s mTOR inhibitor Afinitor.

One out of four?

Just one dose, 10mg once daily, reduced laboratory-confirmed infections versus placebo at week 16 to a level of statistical significance below p=0.05. The twice-daily dose, as well as the Afinitor combo, performed numerically worse than control.

RTB101 is a dual PI3K/mTOR inhibitor that Restorbio now describes as acting on the TORC1 but not TORC2 multiprotein complex. Preclinically TORC1 inhibition has been shown to prolong lifespan, leading to a postulated role of mTOR inhibitors like sirolimus as anti-ageing therapeutics.

Two mTOR inhibitors might be thought to be better than one, and on an analyst call Restorbio said a benefit in combination with Afinitor had previously been seen, but that was in a trial of less sick patients. The only explanation for the combo’s failure today was that “less TORC1 inhibition ... may have greater benefit in high-risk elderly patients”.

This could also help explain the failure of the 10mg twice daily dose, but it does nothing to clarify why 5mg once daily did not work either; the p value for this dose was a non-significant 0.108.

And there are more red flags in the dataset, not least that the company used a one-sided p value to generate the purported 10mg once daily win at p=0.026. A threshold of 0.05 for a one-sided p value clearly makes

statistical significance twice as likely to be hit than if applying a two-sided p value threshold of 0.05.

Using two-sided p values is standard industry practice unless there are strong scientific arguments to the contrary – and Restorbio provided none.

The company also seems to have used a modified intent-to-treat analysis, saying it counted only those patients who received at least a partial dose of study drug, rather than all-comers.

And it confirmed that to get the 0.026 p value it had to combine both parts of the trial; analysis of just part two did not meet significance, it told analysts. It would not say whether the p value was adjusted for multiplicity or for the fact an interim analysis had earlier taken place, to allow part two to proceed.

VCs celebrate

At least Restorbio's directors and venture investors will be happy with the data. They agreed to a 180-day trading lock-up as part of the January 26 flotation, and this lock-up expired today.

This means that if they wished to sell any of their pre-IPO stakes they could today exit into a sharply rising market: Restorbio surged 180% in the premarket, and was still up 70% in early trade. VCs include Puretech Health, which founded Restorbio and retains a 35% stake.

Puretech orchestrated Restorbio's purchase of RTB101 from Novartis, which had tested the asset's ability to improve response rates to flu vaccination. Reducing infections in the elderly could be seen as a new use, but whether today's data back a "clear path forward" for the 10mg once-daily dose, as Restorbio insists, now lies in the hands of the FDA.